NEW SYSTEMIC TREATMENT OPTIONS FOR RADIOIODINE-REFRACTORY DIFFERENTIATED AND MEDULLARY THYROID CANCERS

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INTRODUCTION TO DIFFERENTIATED (DTC) AND MEDULLARY (MTC) THYROID CANCERS

Epidemiology
Histology
Molecular Biology
Radioiodine Refractoriness in DTC
LEARNING OBJECTIVES

To better understand the genetic landscape of the different subtypes of thyroid cancer.

To review the current treatment options for patients with differentiated thyroid cancer (DTC) and medullary thyroid cancer (MTC).

To improve the knowledge from the upcoming drugs for the treatment of patients with DTC and MTC.
**Epidemiology**

Thyroid cancer represents 1% of all diagnosed tumours in adults

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>233,000</td>
<td></td>
<td>Breast</td>
<td>232,670</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,000</td>
<td>14%</td>
<td>Lung &amp; bronchus</td>
<td>108,210</td>
</tr>
<tr>
<td>Colorectum</td>
<td>71,830</td>
<td>8%</td>
<td>Colorectum</td>
<td>65,000</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,390</td>
<td>7%</td>
<td>Uterine corpus</td>
<td>52,830</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>43,890</td>
<td>5%</td>
<td>Thyroid</td>
<td>47,790</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,140</td>
<td>5%</td>
<td>Non-Hodgkin lymphoma</td>
<td>32,530</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,270</td>
<td>4%</td>
<td>Melanoma of the skin</td>
<td>32,210</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>30,220</td>
<td>4%</td>
<td>Kidney &amp; renal pelvis</td>
<td>24,780</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,100</td>
<td>4%</td>
<td>Pancreas</td>
<td>22,890</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>24,600</td>
<td>3%</td>
<td>Leukemia</td>
<td>22,280</td>
</tr>
<tr>
<td>All Sites</td>
<td>855,220</td>
<td>100%</td>
<td>All Sites</td>
<td>810,320</td>
</tr>
</tbody>
</table>

Thyroid cancer annual incidence increases from 2006 to 2010 and was 5.4% in men and 6.5% in women. The rate of death is also increasing from 1992 to 2010, although slightly, from 0.47 (per 100,000 population) to 0.50 among men and from 0.48 to 0.51 among women.

**EPIDEMIOLOGY: DTC AND MTC**

**Differentiated thyroid cancer**
- Recurrent or metastatic disease:
  - $\approx 7$–$23\%$ (5% *de novo*)
- 2/3 RAI- Refractory
- 10-year overall survival:
  - 75–95% Stage I-II
  - <50–60% Stage III-IV

**Medullary thyroid cancer**
- 50% N+
- M+
  - At diagnosis: 4–17%
  - At follow up 18–38%
- 20% will die from progressive disease
- 10-year overall survival:
  - 95% localised disease
  - 75% regional metastases
  - 40% distant metastases

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Dadu R, Cabanillas ME. Minerva Endocrinol 2012;37:335–56;
HISTOLOGY

DTC represents more than 90% of all thyroid cancers

Differentiated thyroid cancer >90%

Medullary thyroid cancer ≈2%

Anaplastic thyroid cancer <1%

Papillary (80%), Follicular (10–20%), Hürthle (2–8%), Poorly differentiated (2%)
HISTOLOGY

The new WHO classification (2017) has been conducted in concordance with the genetic-molecular characterisation of these tumours

**WHO classification for differentiated follicular-derived thyroid carcinomas**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Morphology</th>
<th>Molecular markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIFTP</td>
<td>Encapsulated, clear nuclei, no papillae</td>
<td>RAS, BRAF K601E</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tall, columnar, solid, hobnail variants</td>
<td>Papillae and clear nuclei</td>
<td>BRAF V600E, RET/PTC fus, NTRK fus, ALK fus, 1q amp</td>
</tr>
<tr>
<td></td>
<td>Follicles and clear nuclei</td>
<td>BRAF K601E, RAS, PAX8/PPARγ, EIF1AX, THADA fus, 22q del</td>
</tr>
<tr>
<td></td>
<td>Special structural and cell features</td>
<td>BRAF V600E, 1q amp, TERT promoter, TP53, PIK3CA, CTNNB1</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>Capsular invasion (MI), vascular invasion &gt;4</td>
<td>RAS, PAX8/PPARγ, PTEN, PIK3CA, TSHR, TERT promoter, CNA</td>
</tr>
<tr>
<td>blood vessels (angioinvasive), Extrathyroidal invasion (WI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hürthle cell carcinoma</td>
<td>Capsular invasion (MI), vascular invasion &gt;4</td>
<td>RAS, EIF1AX, PTEN, TP53, CNA, mtDNA</td>
</tr>
<tr>
<td>blood vessels (WI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>Invasion, mitoses &gt;3, necrosis, #convoluted nuclei</td>
<td>RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus, histone methyltransferases, SWI/SNF chromatin remodeling complex</td>
</tr>
</tbody>
</table>
**HISTOLOGY**

Dominant signalling pathways associated with thyroid cancers

Model of the progression of thyroid tumorogenesis by the activation of MAPK and PI3K/AKT pathways through the accumulation of genetic alterations

MOLECULAR BIOLOGY: DTC

Integrated genomic characterisation of papillary thyroid carcinoma (PTC)

Key messages from the genomic analysis of 496 PTC:

- 80% of driver genetic alterations involve 3 genes: \textit{BRAF, RAS} (\textit{NRAS, KRAS}) and \textit{RET}
- Dark matter reduction from 25% to 3%
- Novel genetic aberrations in known genes (\textit{BRAF} fusions)
- Novel genes with driver alterations (\textit{TERT, CHEK2, PPM1D, EIF1AX})
- Low proportion of copy number alterations (27.2%), more frequent in follicular variant
- Low somatic mutation density (average: 0.41 nonsynonymous mutations per Mb)
MOLECULAR BIOLOGY: PTC
Signalling and differentiation

Molecular Biology: PTC
Signalling and differentiation → Results in profound phenotypic differences

<table>
<thead>
<tr>
<th></th>
<th>BRAF-like</th>
<th>RAS-like</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signalling</strong></td>
<td>High MAPK</td>
<td>MAPK and PI3K/AKT (p90RSK as a crucial crossroad)</td>
</tr>
<tr>
<td><strong>Genetic alterations</strong></td>
<td>BRAF V600E, RET fusions, BRAF fusions</td>
<td>NRAS, HRAS, KRAS, EIF1AX, PAX8/PPAR</td>
</tr>
<tr>
<td><strong>Histological variants</strong></td>
<td>Classical, tall cell</td>
<td>Follicular</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td>Low/Heterogeneous</td>
<td>High</td>
</tr>
<tr>
<td><strong>Risk of recurrence</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>miRNA</strong></td>
<td>miR-21, miR-146b, miR-204, miR-221/222</td>
<td>miR-183-5p, miR-182-5p</td>
</tr>
</tbody>
</table>
The main driver mutations are RET and RAS.

RET activation leads to the activation of the MAPK and PI3K pathways that regulate cell proliferation and survival:

- **Germline RET mutations**: MTC is associated with familial syndromes in 30% of patients
  - MEN2A phenotype is linked to mutations in RET cysteine codons in exons 10 and 11
  - MEN2B phenotype is almost exclusively associated with the Met918Thr alteration in exon 16
- **Somatic RET mutations**: reported in ≈50% of patients with sporadic MTC
  - The most common alteration is Met918Thr in exon 16

RAS activation has been reported in 10–45% of patients with sporadic MTC (more commonly HRAS and KRAS) and in 80% of patients RET-negative sporadic MTC.

VEGFR, MET and FGFR are overexpressed in MTC.

MOLECULAR BIOLOGY: SPORADIC VS. HEREDITARY MTC


MOLECULAR BIOLOGY: MTC

Intracellular signalling pathways activated by RET

SYSTEMIC TREATMENT FOR RAI-DTC AND MTC

Lenvatinib and Sorafenib
Vandetanib and Cabozantinib
RET inhibitors: Pralsetinib, Selpercatinib
Other novel therapeutic strategies
SYSTEMIC TREATMENT

In thyroid cancer, some signalling pathways have shown potential therapeutic relevance.
SYSTEMIC TREATMENT
Approved drugs in DTC and MTC

<table>
<thead>
<tr>
<th></th>
<th>DTC</th>
<th>MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LENVATINIB</td>
<td>VANDETANIB</td>
</tr>
<tr>
<td></td>
<td>SORAFENIB</td>
<td>CABOZANTINIB</td>
</tr>
<tr>
<td>SELPERCATINIB*</td>
<td>SELPERCATINIB*</td>
<td></td>
</tr>
</tbody>
</table>

*FDA approval (May 2020) for adult and pediatric patients ≥ 12 years of age with advanced or metastatic RET-mutant MTC or RET-fusion RAI-DTC who require systemic therapy. [link](https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions)
SYSTEMIC TREATMENT FOR DTC
ESMO Clinical Practice Guidelines

Recommendations for management of RAI-refractory, advanced/metastatic DTC patients
SYSTEMIC TREATMENT FOR RAI-DTC: SORAFENIB

N=417
- Locally advanced or metastatic, RAI-refractory DTC
- Progression (RECIST) within the previous 14 months
- No prior chemotherapy, targeted therapy, or thalidomide

Stratified by:
- Geographical region (North America or Europe or Asia)
- Age (<60 or ≥60 years)

Progression assessed by independent central review every 8 weeks
At progression
- Patients on placebo allowed to cross over at the investigator’s discretion
- Patients on sorafenib allowed to continue on open-label sorafenib at the investigator’s discretion

Primary endpoint
- Progression-free survival

Secondary endpoints
- Overall survival
- Response rate
- Safety
- Time to progression
- Disease control rate
- Duration of response
- Sorafenib exposure (AUC0-12)

Randomisation 1:1
Sorafenib
400 mg orally twice daily
Placebo
Orally twice daily

Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 3 Trial, 319-28, Copyright 2014, with permission from Elsevier.

mPFS = 10.8 m (S) vs. 5.8 m (P); HR 0.59 (95% CI: 0.45, 0.76; p=0.0001)

Reprinted from The Lancet, 384(9940), Brose M, et al. Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 3 Trial, 319-28, Copyright 2014, with permission from Elsevier.
## SYSTEMIC TREATMENT FOR RAI-DTC

Other secondary efficacy endpoints

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib n (%)</th>
<th>Placebo n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total evaluable patients</td>
<td>196</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>Response rate</td>
<td>24 (12.2)</td>
<td>1 (0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (12.2)</td>
<td>1 (0.5)</td>
<td>—</td>
</tr>
<tr>
<td>Stable disease for ≥6 months</td>
<td>82 (41.8)</td>
<td>67 (33.2)</td>
<td>—</td>
</tr>
<tr>
<td>Disease control rate (CR + PR + SD ≥6 months)</td>
<td>106 (54.1)</td>
<td>68 (33.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median duration of response (PRs) months (range)</td>
<td>10.2 (7.4–16.6)</td>
<td>NA</td>
<td>—</td>
</tr>
</tbody>
</table>
## SYSTEMIC TREATMENT FOR RAI-DTC

### Safety

<table>
<thead>
<tr>
<th>AE, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sorafenib (n=207)</th>
<th>Placebo (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>76.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Alopecia</td>
<td>67.1</td>
<td>0</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>50.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Weight loss</td>
<td>46.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Metabolic/lab (other)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35.7</td>
<td>0</td>
</tr>
<tr>
<td>Serum TSH increase&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>31.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>23.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>21.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20.8</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>18.8</td>
<td>9.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Treatment-emergent adverse events occurring in ≥10% of patients in either arm during the double-blind period (safety population); <sup>b</sup>TSH levels >0·5 mIU/L are included within this NCI CTCAE term and blood TSH increase (MedDRA v15·1 term) is also reported.

SYSTEMIC TREATMENT FOR RAI-DTC: LENVATINIB

Patients with DTC (N=392)
- IRR evidence of progression within previous 13 months
- $^{131}$I-refractory disease
- Measurable disease
- Up to 1 prior VEGF or VEGFR-targeted therapy

Stratification
- Geographic region (Europe, N. America, other)
- Prior VEGF/VEGFR-targeted therapy (0,1)
- Age (≤65 years, >65 years)

Lenvatinib (n=261)
24 mg daily PO

Randomisation 2:1

Placebo (n=131)
24 mg daily PO

Treatment until disease progression confirmed by IRR (RECIST v1.1)

Primary endpoint
PFS

Secondary endpoints
ORR
OS
Safety

Lenvatinib
(Optional, open-label)

SYSTEMIC TREATMENT FOR RAI-DTC

mPFS = 18.3 m (L) vs. 3.6 m (P); HR 0.21 (99% CI: 0.14, 0.31; p<0.001)

SYSTEMIC TREATMENT FOR RAI-DTC
Other secondary efficacy endpoints

ORR = 64.8% (L) vs. 1.5% (P)
OR 28.87 (95% CI: 12.46, 66.86; p<0.001)

## SYSTEMIC TREATMENT FOR RAI-DTC

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Lenvatinib (n=261)</th>
<th>Placebo (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68</td>
<td>42</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue / asthenia</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>
**SYSTEMIC TREATMENT FOR RAI-DTC**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Sorafenib</th>
<th>Lenvatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reduction</td>
<td>133 (64.3%)</td>
<td>177 (68%)</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>137 (66.2%)</td>
<td>215 (82%)</td>
</tr>
<tr>
<td>Discontinuation of treatment</td>
<td>39 (18.8%)</td>
<td>37 (14%)</td>
</tr>
<tr>
<td>Fatal AE treatment-related (investigator)</td>
<td>1 (0.4%)</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

- **Myocardial infarction (n=1)**
- **Pulmonary embolism (n=1)**
- **Hemorrhagic stroke (n=1)**
- **General health deterioration (n=4)**

SYSTEMIC TREATMENT FOR RAI-DTC

The mutational status BRAF/RAS does not have a role as a predictive factor.

**SELECT trial**

<table>
<thead>
<tr>
<th>Mutational Status</th>
<th>Treatment</th>
<th>Lenvatinib</th>
<th>Placebo</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF+</td>
<td>NE</td>
<td>4.3 months</td>
<td>HR 0.17</td>
<td></td>
</tr>
<tr>
<td>BRAF-</td>
<td>18.3 months</td>
<td>1.9 months</td>
<td>HR 0.15</td>
<td></td>
</tr>
<tr>
<td>RAS+</td>
<td>NE</td>
<td>5.6 months</td>
<td>HR 0.12</td>
<td></td>
</tr>
<tr>
<td>RAS-</td>
<td>18.3 months</td>
<td>2.4 months</td>
<td>HR 0.20</td>
<td></td>
</tr>
</tbody>
</table>

**DECISION trial**

<table>
<thead>
<tr>
<th>Mutational Status</th>
<th>Treatment</th>
<th>Lenvatinib</th>
<th>Placebo</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF+</td>
<td>20.5 months</td>
<td>9.4 months</td>
<td>HR 0.46</td>
<td></td>
</tr>
<tr>
<td>BRAF-</td>
<td>8.9 months</td>
<td>3.8 months</td>
<td>HR 0.55</td>
<td></td>
</tr>
<tr>
<td>RAS+</td>
<td>5.5 months</td>
<td>3.4 months</td>
<td>HR 0.49</td>
<td></td>
</tr>
<tr>
<td>RAS-</td>
<td>10.8 months</td>
<td>5.7 months</td>
<td>HR 0.60</td>
<td></td>
</tr>
</tbody>
</table>

All patients benefited from Lenvatinib or sorafenib regardless of mutational status.

SYSTEMIC TREATMENT FOR MTC
ESMO Clinical Practice Guidelines

**Primary endpoint:** Progression-free survival

**Secondary endpoints:** Objective response rate, disease control rate at 24 weeks, duration of response, overall survival, biochemical response (decreases in CTN and CEA), time to worsening of pain

PFS = 19.3 m vs. NR (estimated 30.5 m); HR 0.46 (95% CI: 0.31, 0.69; p<0.001)
SYSTEMIC TREATMENT FOR MTC

Forest plot of HR for PFS according to RET mutation status and M918T mutation status in sporadic MTC

In patients with sporadic MTC:
- RET mutation-positive (M918T) patients show a benefit in PFS and RR with vandetanib
- Small number of patients RET mutation-negative and large number of RET mutation-unknown ➔ subgroup analysis of PFS and RR resulted inconclusive

RR=54.5%
RR=30.9%

SYSTEMIC TREATMENT FOR MTC: CABOZANTINIB

Unresectable locally advanced/metastatic MTC with documented RECIST progression within previous 14 months
N=330

Cabozantinib 140 mg/24 hr
n=219

Placebo
n=111

PROGRESSION FREE SURVIVAL
Disease progression per mRECIST or death

Randomisation 2:1

Primary endpoint: Progression-free survival mRECIST determined by IRC
Secondary endpoints: Overall survival, objective response rate and assessment of the relationship between RET mutation status and efficacy of cabozantinib
SYSTEMIC TREATMENT FOR MTC

PFS 11.2 m vs. 4.0 m; HR 0.28 (95% CI: 0.19, 0.40; p<0.001)

SYSTEMIC TREATMENT FOR MTC

Subgroup analysis of OS and PFS according to RET mutation status, RET M918T status, and RAS mutations status


Cabozantinib was favoured over placebo for both OS and PFS in patients with and without RET mutations and for those with an unknown RET mutation status.
### SYSTEMIC TREATMENT FOR MTC

<table>
<thead>
<tr>
<th>PHASE 3 trials</th>
<th>ZETA¹</th>
<th>EXAM²</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>331</td>
<td>330</td>
</tr>
<tr>
<td>Treatment</td>
<td>Vandetanib</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Unresectable locally advanced/metastatic</td>
<td>Documented RECIST progression</td>
</tr>
<tr>
<td>RET⁺ / RET⁻ / RET unknown</td>
<td>56% (187) / 2.4% (8) / 41% (136)</td>
<td>48% (159) / 12% (41) / 39% (130)</td>
</tr>
<tr>
<td>ORR</td>
<td>45% vs. 13%</td>
<td>28% vs. 0%</td>
</tr>
<tr>
<td>DCR</td>
<td>87% vs. 71%</td>
<td>55.3% vs. 13.5%</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>69% vs. 3% (p&lt;0.001)</td>
<td>-45.2% vs. +57.2% (p&lt;0.001)</td>
</tr>
<tr>
<td>CEA</td>
<td>52% vs. 2% (p&lt;0.001)</td>
<td>-23.7% vs. +88.7% (p&lt;0.001)</td>
</tr>
<tr>
<td>PFS</td>
<td>NR (predicted median 30.5 months) vs. 19.3 months (HR 0.27)</td>
<td>11.2 months vs. 4.0 months (HR 0.28)</td>
</tr>
<tr>
<td>OS</td>
<td>HR 0.83 (95% CI: 0.60, 1.14)</td>
<td>HR 0.85 (95% CI: 0.64, 1.12)</td>
</tr>
<tr>
<td>Adverse events ≥G3</td>
<td>Diarrhoea, hypertension, QTc prolong, fatigue</td>
<td>Diarrhoea, PPE, hypertension fatigue</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>12% vs. 3%</td>
<td>16% vs. 8%</td>
</tr>
</tbody>
</table>

NR, not reached; PPE, palmar-planter erythrodysesthesia.
### SYSTEMIC TREATMENT FOR MTC: OTHER VEGFR-TKI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>N</th>
<th>RET mutation status</th>
<th>PFS (months)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axitinib</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Phase II</td>
<td>11 (60 DTC+MTC)</td>
<td>-</td>
<td>18 (DTC+MTC)</td>
<td>HTN, fatigue, GI, anorexia, proteinuria</td>
</tr>
<tr>
<td><strong>Sorafenib</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Phase II</td>
<td>16 + 5 (S + H)</td>
<td>10/12 + 5/5</td>
<td>17.9</td>
<td>Diarrhoea, oral pain, PPE, alopecia, HTN</td>
</tr>
<tr>
<td><strong>Sunitinib</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Phase II</td>
<td>25</td>
<td>11/13 (85%)</td>
<td>-</td>
<td>Asthenia, GI, PPE, Neu, Linf</td>
</tr>
<tr>
<td><strong>Motesanib</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Phase II</td>
<td>91</td>
<td>33/47</td>
<td>12</td>
<td>Diarrhoea, HTN, fatigue, anorexia</td>
</tr>
</tbody>
</table>


PPE, palmar-plantar erythrodysesthesia.
NEW DRUGS IN THE FIELD OF DTC AND MTC: RET INHIBITORS

RET mutations in MTCs:
- M918T = 70.5%
- C634R = 4.9%
- A993F = 2.2%
- C634Y = 2.1%
- C634W = 1.9%
- C630R = 1.5%
- E632_L633 del = 1.4%
- D999_E901 del = 1.4%
- C620R = 0.6%
- S991A = 0.6%

RET rearrangements occur in up to 10–20% of PTCs:
- CCDC6 = 59%
- NCOA4 = 36%

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

Preclinical and clinical activity, IC50, and efficacy of multikinase versus selective RET Inhibitors in MTC

<table>
<thead>
<tr>
<th>Drug</th>
<th>RET</th>
<th>IC50, nM</th>
<th>CCDC6-RET</th>
<th>VEGFR2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT</td>
<td>M918T</td>
<td>V804L</td>
<td>V804M</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>4</td>
<td>7</td>
<td>3,597</td>
<td>726</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>11</td>
<td>8</td>
<td>45</td>
<td>162</td>
</tr>
<tr>
<td>LOXO-292</td>
<td>0.4</td>
<td>0.7</td>
<td>-</td>
<td>0.8</td>
</tr>
<tr>
<td>BLU-667</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER
LIBRETTO – 001: Phase 1/2 trial in patients with RET-altered cancers


RET alteration
- Determined by local CLIA (or similarly accredited laboratories)
Primary endpoint
- Objective response rate (RECIST 1.1)
Secondary endpoints
- Duration of response
- PFS
- Safety
Treatment beyond progression permitted with continued benefit

Phase 1 dose escalation
Selpercatinib dosed at 20 mg QD-240 mg BID

Phase 2 dose escalation
Selpercatinib dosed at 160 mg BID

Total enrolled
- n=531

RET-mutant medullary thyroid cancer
- n=226

RET fusion-positive thyroid cancer
- n=27

RET fusion-positive NSCLC
- n=253

Other
- n=25

Prior carbozatinib and/or vandetanib
- n=214

Cabozatinib/vandetanib-naïve
- n=88

Non-measurable disease
- n=14

Primary analysis set
- n=55

First 55 patients with RET-mutant MTC who had received prior cabozatinib and/or vandetanib*
DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER
LIBRETTO – 001: Activity of selpercatinib in RET-mutant MTC primary analysis set (N=55)

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding. Wirth L, et al. Ann Oncol 2019:30 (suppl_5):v933. Presented at ESMO; abstract LBA93; with permission from Dr L. Wirth.
DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER
LIBRETTO – 001: Activity of selpercatinib in RET fusion-positive thyroid cancer (N=26)

Investigator response assessments as of June 17, 2019. Total % may be different than the sum of the individual due to rounding.
## DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER
### LIBRETTO – 001: Updated results from selpercatinib in RET-mutant MTC and RET fusion+ TC

### Table: Response and Survival Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RET-mutant MTC</th>
<th>Previously-Treated RET Fusion+ Thyroid Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent Review</td>
<td>Investigator Assessment</td>
</tr>
<tr>
<td></td>
<td>(n=55)</td>
<td>(n=55)</td>
</tr>
<tr>
<td><strong>Objective response rate, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>69 (53–61)</td>
<td>62 (46–75)</td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (60)</td>
<td>31 (56)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>14 (26)</td>
<td>16 (29)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (4)**</td>
<td>2 (4)**</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Censored, n (%)</td>
<td>32 (84)</td>
<td>25 (74)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>NE (19–NE)</td>
<td>NE (16–NE)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td><strong>Progression-free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Censored, n (%)</td>
<td>42 (76)</td>
<td>33 (60)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>NE (24–NE)</td>
<td>27 (14–NE)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>1-year PFS rate, % (95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- *Includes 3 patients with unconfirmed partial responses pending confirmation.
- **Includes 1 patient who died prior to their first response assessment.
- Includes only confirmed responses.
- *Unstable median, based on fewer than 10% of total number of events. Total % may be different than the sum of the individual components due to rounding. Abbreviations: NE, not estimable; PFS, progression-free survival.

DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

ARROW STUDY: a Phase 1 dose followed by a Phase 2 expansion (400 mg QD) in patients with advanced RET-altered solid tumours

Phase 2 study design
- Advanced solid tumours
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

Pralsetinib dosing: 400 mg PO QD

Primary endpoints
- Centrally reviewed ORR per RECIST v1.1
- Safety
DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

ARROW STUDY: a Phase 1 dose followed by a Phase 2 expansion (400 mg QD) in patients with advanced RET-altered solid tumours

**MTC (N=49)**

All RET mutant MTC patients (400 mg QD) per central radiology

74% ORR* in treatment naïve RET-mutated MTC and 60% ORR‡ in those previously treated

**DTC (N=11)**

Data reported on April 1, 2020.

Subbiah V, et al. J Clin Oncol 38:2020 (suppl; abstr 109); with permission from Dr V Subbiah.
DEVELOPMENT OF RET INHIBITORS IN THYROID CANCER

Safety

Selpercatinib:\textsuperscript{1}

The most frequent treatment-related AEs (≥15%) were dry mouth (33%), increased AST (26%), hypertension (24%), increased ALT (25%), diarrhoea (22%) and fatigue (18%).

Pralsetinib:\textsuperscript{2}

The most frequent treatment-related AEs (≥15%) were anaemia (33%), increased AST (33%), decreased WBC count (33%), hypertension (30%), increased ALT (26%), hyperphosphatemia (19%) and neutropenia (19%).

NTRK INHIBITORS IN THYROID CANCER

NTRK1-3 (Neurotrophic Tyrosine Receptor Kinase): Encoding for transmembrane Tropomyosin Receptor Kinase: TRKA, TRKB, TRKC.

**Physiologic functions:** Differentiation and survival of neurons, synapse formation and plasticity, membrane trafficking, formation of axons and dendrites

NTRK gene fusions are targetable genetic alterations that code for fusion proteins that lead constitutive activation of signalling pathways

Thyroid cancer has a frequency of TRK fusions between 5–25%

First-generation TRK inhibitors: Larotrectinib and entrectinib

NTRK INHIBITORS IN THYROID CANCER

ENTRECTORINIB: Analysis of three Phase 1/2 trials
N=54 (Thyroid n=5)

- ORR = 57% (CR = 7%)
- PD = 7%
- mPFS = 11.2 months (8.0, 14.9)

LAROTRECTINIB: Analysis of three Phase 1/2 trials
N=153 (Thyroid n=24)

- ORR = 79% (CR = 16%) → Thyroid (ORR = 79%)
- PD = 6%
- mPFS = 18.3 months (22.1, NE)

REDIFFERENTIATION THERAPY IN THYROID CANCER (DTC)

NIS (sodium iodide symporter) mediates radioiodine uptake into thyroid normal and cancer cells

Alterations in RTK/BRAF/MAPK/ERK and PI3K/AKT/mTOR pathways underly the diminished NIS signaling; key in RAI refractoriness.

Kinase inhibitors have been shown to re-induce iodide uptake in RAI-refractory thyroid cancer cells

Aashiq M, et al. Cancers 2019;11:1382–97. Reproduced under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/; accessed July 2020)
REDIFFERENTIATION THERAPY IN THYROID CANCER (DTC)

1. Selumetinib 75 mg/12 h x 4 w

<table>
<thead>
<tr>
<th>Tumour genotype</th>
<th>Patients with increased iodine uptake in a lesion after selumetinib</th>
<th>Patients who received radioiodine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Total no. of patients</td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>4/9</td>
<td>1/9</td>
</tr>
<tr>
<td>NRAS</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>RET/PTC</td>
<td>2/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Wild-type</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12/20</strong></td>
<td><strong>8/20</strong></td>
</tr>
</tbody>
</table>

2. Dabrafenib 150 mg/12 h x 25 d

N=10 BRAF-mutated RAI PTC

This strategy is currently under research:
NCT01947023: Dabrafenib + Lapatinib
NCT03244956: Dabrafenib + Trametinib

IMMUNOTHERAPY IN THYROID CANCER

Rationale in thyroid cancer

Antithyroid antibodies are present in 18–40% of patients with PTC

Recruitment of mast cells has been related with dedifferentiation, invasion and angiogenesis through production of chemokines or interleukin

Tregs have been identified in large amounts in DTC and ATC, associated with tumour aggressiveness

Tumour-associated macrophages (TAM): Presence of M2 TAM in DTC were associated with invasion and poor prognosis

Immune profiling of BRAF-V600E-positive DTC compared with BRAF wild-type tumours:

- High levels of PD-L1 (53% vs. 12.5%)
- High levels of HLA G (41% vs. 12.5%)
- High levels of suppressive T cell and macrophage components

Angell TE, et al. Thyroid 2014;24:1385–93;
IMMUNOTHERAPY IN THYROID CANCER

Immunotherapy trials addressing thyroid cancer: Phase Ib KEYNOTE-028 trial

Pembrolizumab in Papillary and Follicular thyroid cancer (N=22)

ORR = 2%
Clinical Benefit Rate = 50% (95% CI: 28, 72)
SD ≥6 months = 69% (95% CI: 39, 91)

Mehnert JM, et al. BMC Cancer 2019;19(1):196. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0; accessed July 2020).
**IMMUNOTHERAPY IN THYROID CANCER**

Immunotherapy trials addressing thyroid cancer

<table>
<thead>
<tr>
<th>NCT IDENTIFIER</th>
<th>TARGET</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01346358</td>
<td>TAM</td>
<td>CSF-1R inhibitor</td>
</tr>
<tr>
<td>NCT01525602</td>
<td>TAM</td>
<td>CSF-1R inhibitor + paclitaxel</td>
</tr>
<tr>
<td>NCT01856920</td>
<td>Dendritic cells</td>
<td>GI-6207 (vaccine targeting CEA in MTC)</td>
</tr>
<tr>
<td>NCT02239861</td>
<td>Dendritic cells</td>
<td>Specific adoptive cytotoxic T cells targeting several tumour antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NY-ESO-1, MAGEA4, PRAME, surviving, SSX)</td>
</tr>
<tr>
<td>NCT02054806</td>
<td>T cells</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>NCT02452424</td>
<td>TAM</td>
<td>CSF-1R inhibitor + pembrolizumab</td>
</tr>
<tr>
<td>NCT02718911</td>
<td>TAM</td>
<td>CSF-1R inhibitor + tremelimumab + durvalumab</td>
</tr>
<tr>
<td>NCT03753919</td>
<td>T cells</td>
<td>Tremelimumab + durvalumab</td>
</tr>
<tr>
<td>NCT02501096</td>
<td>T cells</td>
<td>Lenvatinib + pembrolizumab</td>
</tr>
<tr>
<td>NCT01988896</td>
<td>T cells</td>
<td>Cobimetinib + atezolizumab</td>
</tr>
<tr>
<td>NCT01656642</td>
<td>T cells</td>
<td>Vemurafenib + atezolizumab</td>
</tr>
</tbody>
</table>

NOVEL DRUGS

MAPK and PI3K pathways cross talk and tumour escape mechanism

**Targeting ERBB-HER2/3**
- Lapatinib + dabrafenib (NCT01947023)
- Neratinib (NCT03065387)

**Targeting ALK translocations**
- Ceritinib (NCT02289144)

**Targeting mTOR**
- Sorafenib + everolimus (NCT02143726)

**SSTR targeting**
- 177-Lu-PP-F11N (NCT02088645)

**MEK targeting**
- Selumetinib (NCT01843062)
- Dabrafenib + trametinib (NCT02034110)

Naoum GE, et al. Molecular Cancer 2018;17(1):51. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0; accessed July 2020).
CONCLUSIONS

Thyroid carcinoma is a heterogeneous disease, but the advances in understanding the genomic landscape have helped in the development of novel drugs.

Multikinase inhibitors that block VEGFR signalling have demonstrated benefit for DTC and MTC in Phase 3 trials, such as sorafenib, lenvatinib, cabozantinib and vandetanib.

The scenario of thyroid cancer treatment is rapidly changing with the role of RET inhibitors, such as pralsetinib and selpercatinib.

Other promising targets are under research based on the molecular biology of thyroid cancer and resistance mechanisms.
THANK YOU!